#46 Appeal Brief

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PATENTS

Attorney Docket No.: BD1 CIP FWC IV

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Sherie L. Morrison, et al.
Serial No.	:	08/266,154
Filed	:	June 27, 1994
For	:	RECEPTORS BY DNA SPLICING AND EXPRESSION
Group Art Unit	:	1806
Examiner	:	T. Nisbet

Palo Alto, California
September 25, 1996

Honorable Assistant Commissioner
of Patents
Washington, D.C. 20231

AMENDED APPEAL BRIEF

Sir:

Pursuant to 37 C.F.R. § 1.192, and in response to the communication from the Examiner mailed August 26, 1996, applicants file this Amended Appeal Brief. The Notice of Appeal was filed December 13, 1995.

Applicants have petitioned concurrently herewith for a four month extension of time for appeal up to and including June 13, 1996 and have paid the required fee of $1,400.00. Applicants authorize the Commissioner to charge Deposit Account No. 06-1075 the amount of $290.00 in payment of the filing fee for this Brief under 37 C.F.R.

§ 1.17(f). Applicants also request an oral hearing before the Board of Patent Appeals and Interferences and authorizes the Commissioner to charge Deposit Account No. 06-1075 the amount of $250.00 for that request. The Commissioner is also authorized to charge any additional fees that may be due, or credit any overpayment, to Deposit Account No. 06-1075.

In view of the arguments and authorities set forth below, this Board should find the final rejection of claims 39-41, 43-48, 54-55, 57-58, 60-69 and 71-95 of this application to be in error and should reverse that rejection.

REAL PARTIES IN INTEREST

The inventors are Sherie L. Morrison, Ph.D., Leonard L. Herzenberg, Ph.D. and Vernon T. Oi, Ph.D. At the time they made this invention, Dr. Morrison was Associate Professor of Microbiology at Columbia University, Dr. Herzenberg was a Professor in the Department of Genetics at Stanford University and Dr. Oi was a post-doctoral scientist in Dr. Herzenberg's laboratory. This application is assigned to Stanford University and Columbia University and has been licensed to Centocor.

RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to appellants, the appellant's legal representative, or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

STATUS OF THE CLAIMS

Appellants appeal from the final rejection of claims 39-41, 43-48, 54-55, 57-58, 60-69 and 71-95 by notice of appeal filed December 13, 1995. Claims 1-38, 42, 49-53, 56, 59, and 70 have been canceled. No claims have been allowed. The claims on appeal are set forth in Appendix A.

STATUS OF AMENDMENTS

No amendments were filed subsequent to the final rejection.

SUMMARY OF INVENTION

This invention is a method of producing functional antibodies that are capable of specifically binding antigen. The method consists of producing antibodies comprising a heavy chain and light chain directly from mammalian host cells without need for additional steps outside the host cell, by

> transfecting non-antibody producing mammalian cells with DNA sequences coding for antibody light and heavy protein chains, and
>
> maintaining the cells in a medium in which the cells express those sequences to produce the chains, assemble antibodies from those chains, and secrete the functional antibodies.

Specification serial no. 06/664,473, p. 2 ln. 2 to p. 31 ln. 15, and p. 14 ln. 22 to p. 20 ln. 34). The transfection step may be carried out by separately transfecting host cells with a DNA sequence coding for either the light or heavy chain and then with the DNA sequence for the other chain. The method may also be practiced by transfecting host cells in a single

step with a plasmid or vector containing both the light and heavy chain DNA sequences. However, the fundamental advance of this method is the use of co-expression of the antibody light and heavy chains in mammalian cells to produce large quantities of properly assembled, and thus fully functional, antibodies. Prior to this invention, co-transfection and co-expression of light and heavy antibody chain genes had been done only in bacterial cells with subsequent processing of the protein chains to produce minute yields of antibody.

ISSUE FOR REVIEW

Based on the final rejection, the issue is whether the Examiner erred in rejecting the claims under 35 U.S.C. § 103 as unpatentable over three Cabilly references in view of one Gillies article.

GROUPING OF CLAIMS

On this appeal, the claims stand together.

EXAMINER'S BASIS FOR REJECTION

This appeal involves a single rejection. As summarized in the final rejection dated June 13, 1995, all claims "are rejected under 35 U.S.C. § 103 as being unpatentable over Cabilly (L, R, or 2A) in view of Gillies (Cell 1983)." The final rejection says the rejection is maintained for reasons given in three earlier examiner actions.* A copy of the

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* Those earlier rejections are paper 5 mailed November 29, 1988 in application 07/090,669 (Appendix C), paper 7 mailed May 26, 1989 in application 07/090,669 (continued...)

final rejection is attached as Appendix B, and those three prior examiner actions are attached as Appendices C, D and E. The alleged prior art references are the following:

"Cabilly 2A" is U.S. Patent 4,816,567 issued March 28, 1989 entitled "Recombinant Immunoglobulin Preparations" to S. Cabilly and others based on an application filed April 8, 1983 (See Examiner's Action mailed May 24, 1989, Paper 7);

"Cabilly L" is a European Patent Application published as no. 0125023 on November 14, 1984 by S. Cabilly and others (See Examiner's Action mailed November 29, 1988, Paper 5);*

"Cabilly R" is S. Cabilly and others, Generation of antibody activity from immunoglobulin polypeptide chains produced in *Escherichia coli*, PNAS, Vol. 81, pp. 3273-77 (June 1984) (See Examiner's Action November 29, 1988, Paper 5);

"Gillies S" or "Gillies (Cell 1983)" is Gillies, S., and others, A Tissue-specific Transcription Enhancer Element Is Located in the Major Intron of a Rearranged Immunoglobulin Heavy Chain Gene, Cell, Vol. 33, pp. 717-728 (1983) (See Examiner's Action November 29, 1988, Paper 5.)

A copy of the Cabilly 2A patent is attached as Appendix F and the Gillies article as Appendix G.

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* (...continued)
(Appendix D) and paper 10 mailed September 25, 1990 in application 07/441,189 (Appendix E).

* Cabilly L is a European application claiming priority from the application from which the Cabilly 2A U.S. patent issued and its disclosure is identical to the disclosure of that application. In discussing these two references, we generally will refer and cite to the text of the Cabilly U.S. patent, Cabilly 2A.

ARGUMENT

Introduction

Because the Cabilly L and Cabilly 2A references are identical and Cabilly R is not prior art appellants believe the issue is whether the Examiner erred in rejecting the claims under 35 U.S.C. § 103 based solely on the teachings of effectively one Cabilly reference and the Gillies article.

The record of the prosecution of this and related applications plainly shows that the Examiner had serious doubts about whether the prior art provided the necessary factual basis for this rejection. For example, during prosecution of a divisional application directed to the functional antibodies that are the product of this process, the Examiner finally rejected claims to the antibody and said that, "Applicant's arguments may be persuasive with respect to method but not for product because monoclonal antibodies are synthesized as tetrameres and with proper glycosylation." (Advisory Action dated May 12, 1993 in application 07/771,410, Paper 15; a copy is attached as Appendix H). More revealing is that during prosecution of the parent to this application, appellants' attorney and the Examiner reached agreement with respect to the allowability of the pending claims (Examiner Interview Summary Record, dated December 10, 1993 in application 07/893,610, Paper 31; a copy is attached as Appendix I). In a response about two weeks later, the Examiner withdrew from that agreement, saying:

> "The allowability and subsequent examiner's amendment indicated in the interview summary of Paper No. 31 is hereby withdrawn. Prosecution on the merits of the claims is in response to the Paper No. 29, filed 8/26/93. Any inconvenience to applicant is sincerely regretted." (Examiner's Action dated December 27, 1993 in application 07/893,610, Paper 32)

As appellants will demonstrate, the Examiner was right the first time. In withdrawing his prior decision to allow, the Examiner did not meet the burden of persuasion that he was required to meet to establish that appellants are not entitled to a patent. In re Oetiker, 977 F.2d 1443, 1449, 24 USPQ2d 1443, 1447 (Fed.Cir. 1992) (Plager, J., concurring):

> "An applicant for a patent is entitled to the patent unless the application fails to meet the requirements established by law. It is the Commissioner's duty (acting through the examining officials) to determine that all requirements of the Patent Act are met. The burden is on the Commissioner to establish that the applicant is not entitled under the law to a patent. . . .
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> * * *
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> Specifically, when obviousness is at issue, the examiner has the burden of persuasion and therefore the initial burden of production. Satisfying the burden of production, and thus initially the burden of persuasion, constitutes the so-called prima facie showing. Once that burden is met, the applicant has the burden of production to demonstrate that the examiner's preliminary determination is not correct. The examiner, and if later involved, the Board, retain the ultimate burden of persuasion on the issue.
>
> If as a matter of law, the issue is in equipoise, the applicant is entitled to the patent." [Citations omitted].

The Scope Of The Prior Art

The original application was filed on August 27, 1984 (application 06/644,473).* During prosecution, the applicants showed that they made the invention

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* On August 28, 1987, applicants filed a continuation in part application (07/090,669), that was followed by a series of continuation applications culminating in the current application, 08/266,154 filed June 27, 1994. *After filing the continuation in part application, appellants filed a series of co-pending continuation applications (07/441,189 (November 22, 1989), 07/675,106 (March 25, 1991), 07/893,610 (June 3, 1992)), culminating in the current application.) For purposes of this appeal, the effective filing date of this application is August 27, 1984. The Examiner is in agreement with this effective date, as evidenced by his withdrawal of reliance on the Boss 2B patent as prior art based on applicants' explanation that the claims currently before the Board were entitled to the August 27, 1984 filing date.

prior to the date Ochi, A. et al., PNAS, Vol. 80, pp. 6851-55 (October 1983), was published on October 19, 1983. The final rejection refers to the Cabilly R article, dated June 1984. Because the applicants proved an invention date prior to October 19, 1983, this Cabilly R article is not prior art. Accordingly, the Examiner erred by relying on it.* This means two references must provide the proper factual basis for the rejection under section 103, the Cabilly 2A U.S. patent (or the identical Cabilly L publication) and the Gillies S journal article.

The Cabilly 2A Patent

The Cabilly patent describes a method of producing immunoglobulins using recombinant DNA methods. (col. 1 lns. 7-14). This patent first described immunoglobulins and antibodies, the then-conventional ways to make them, the general procedures to make polypeptides using recombinant DNA technology and the varieties of antibodies and immunoglobulin that might be made with the help of recombinant DNA techniques. (col. 1, lns. 14 to col. 5, ln. 35). The patent described the variety of prokaryotic and eukaryotic cells useful in protein expression systems (col. 8, ln. 62-col. 10, ln. 57), and general methods of constructing vectors and transforming those expression systems with vectors. (col. 10, ln. 58 to col. 11, ln. 47). The patent described one way to obtain a gene sequence coding for the light chain and the heavy chain of an

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* There is no dispute about the adequacy of defendants' proof of invention. The office has accepted that proof and has not relied on the October 19, 1983 Ochi reference. The applicants pointed out in a prior response that the Cabilly R article is not prior art. (Response dated March 13, 1985 in this application 08/266,154, p. 1-2). Because the text of the Examiner's rejections refer to the Cabilly 2A United States patent or to the published Cabilly L European application, we have assumed that the Examiner's continued reference to the Cabilly R article is an oversight and that the Examiner has not and does not rely on it. If the Examiner is relying on that article, that is an error.

antibody through isolation of messenger RNA, preparation of a cDNA library, and probing clones for the sequences which are inserted in appropriate expression vectors. (col. 11, ln. 49 - col. 12, ln. 50).

The patent said the genes coding to the light and heavy chains may be inserted into different expression plasmids or in the same plasmid. (col. 12, lns. 51-56). The light and heavy chain genes may then be transformed into separate cell cultures, separate plasmids containing a light or heavy chain gene used to "co-transform a single cell culture," or a single expression plasmid containing both genes used to transform into a single cell culture. (col. 12, lns. 57-65). The patent then described recovery of the expressed protein. (col. 12, lns. 66-col. 13, lns. 35):

> "Regardless of which of the three foregoing options is chosen, the cells are grown under conditions appropriate to the production of the desired protein. Such conditions are primarily mandated by the type of promoter and control systems used in the expression vector, rather than by the nature of the desired protein. The protein thus produced is then recovered from the cell culture by methods known in the art, but choice of which is necessarily dependent on the form in which the protein is expressed. . . .
>
> When heavy and light chain are coexpressed in the same host, the isolation procedure is designed so as to recover reconstituted antibody. This can be accomplished in vitro as described below, or <u>might be possible in vivo in a microorganism which secretes the IgG chains out of the reducing environment of the cytoplasm.</u> A more detailed description is given in D.2, below." [Emphasis added].

The patent then described in section D.2 the difficulty of combining heavy and light chain proteins into immunoglobulins. The patent described how single chain polypeptides containing the disulfide bonds have been reduced and reoxidized in an effort to generate native structure activity. However, proteins containing more than one chain held together by disulfide bonds had been "more difficult to reconstruct in vitro after reductive cleavage." (col. 13, lns. 36-43). Insulin, one such a protein, had been

reconstructed in that way. (col. 13, lns. 47-50). The patent then described how "[i]mmunoglobulin has proved a more difficult problem than insulin." (col. 13, lns. 51-52). The patent described how this tetrameric molecule was stabilized by fifteen or more disulfide bonds and said that, while it had been possible to recombine light and heavy chains when only interchain disulfide bonds had been eliminated or when fragments of the immunoglobulin such as the "Fab" had been split into light and heavy chains, "[a]ttempts to reconstitute active antibody from fully reduced native IgG have been largely unsuccessful, presumably due to insolubility of the reduced chains and of side products or intermediates in the refolding pathway...." (col. 13, ln. 53-col.14, ln. 2). Given those difficulties, the patent described a "suitable method of immunoglobulin reconstitution" derived from the insulin studies in which the starting material was chemically treated.

The Cabilly patent then contained an example of "Production of Immunoglobulin Chains by *E. coli*." (col. 24, ln. 20-col. 27, ln. 28). In that example, the heavy and light chains of an anti-CEA antibody were expressed, the cells lysed, the resulting light and heavy chain products obtained, and immunoglobulin "reconstituted" for the recombinant chains using the S-sulfonate chemical procedure. (col. 25, ln. 45-col. 26, ln. 37).

The Cabilly patent taught that the DNA sequences for antibody light and heavy chains could be obtained and expressed in a microorganism, the bacterial cell E. coli. Cabilly used those cells to express and produce separate chains. The Cabilly patent is clear that the role of the cell is merely the production of "the desired protein." (col. 12, lns. 66-col. 13, lns. 18). That is why the Cabilly patent was indifferent to whether the chains are expressed in the same cells or in different cells. According to Cabilly, the

chains had to be recombined or reconstituted to form an immunoglobulin or an antibody. Thus, the Cabilly patent only described methods in which the light and heavy chains are expressed, harvested from the cells and then "reconstituted" or "recombined" into an immunoglobulin through subsequent chemical processing. (col. 13, ln. 28-col. 14, ln. 27).

The Cabilly patent does not describe the production of a functional antibody using applicants' claimed method. In particular, Cabilly did not disclose the intracellular assembly of heavy and light chains into antibody and secretion of antibody capable of specifically binding antigen. There is also nothing in the Cabilly patent that teaches or suggests direct production of functional antibodies by non-antibody producing mammalian cells. In fact, in the final rejection, the Examiner has stated that "applicants are correct in characterizing Cabilly's disclosure as non-enabling for myeloma cell production" and that "Cabilly is used only to teach double transfection." The Cabilly patent said that it "might be possible" to design an isolation procedure to recover reconstituted antibody "in vivo in a microorganism which secretes the IgG chains out of the reducing environment of the cytoplasm," but says nothing about even a possibility of producing them directly in mammalian cells. (Emphasis added; col. 13, ln. 19-26).

However, Cabilly's disclosure teaches that co-expression is no better than separate expression of antibody genes. Cabilly describes experimental work in which E. coli were co-transformed with heavy and light chain antibody genes. The double transformants expressed those heavy and light chain genes. However, the Cabilly patent states that only a tiny portion of these chains --0.76%-- could be "recombined" to form anti-CEA antibody. (col. 27, lns. 9-28). In discussing this low degree of recombination in a declaration submitted during prosecution of the application which issued as the Cabilly

patent, one of its inventors explained that the recombination that occurs after heavy and light chains are co-expressed in a bacterial cell is essentially the same as the recombination that occurs after the heavy and light chains are expressed in separate bacterial cells. In the words of the declaration, "[a]s expected, the results with the co-transformant extracts and combined extracts were essentially the same..." (Wetzel Aff., p.2, July 22, 1986, submitted in support of Cabilly's July 24, 1986 Amendment. A copy of that declaration was attached to the Supplemental Preliminary Amendment And Statement, dated May 15, 1991 in application 07/675,106).

Cabilly's bacterial double transformant approach resulted in a minute level of antibody formation -- 0.76% of the chains are reported as having "recombined" to form antibody. (col. 27, lns. 18-27). Cabilly discloses only very limited and slim support for its claim of antigen binding. (col. 26, line 62 - col. 27, line 27). Cabilly does not disclose or enable the production of functional antibodies on a significant scale.

A person skilled in the art would have drawn only one conclusion from the Cabilly patent. Cabilly clearly pointed away from the appellants' process. The appellants conceived and demonstrated a process in which the light and heavy chains are co-expressed in a mammalian cell and that cell directly secreted antibody capable of specific binding to antigen without additional processing. Cabilly does not teach or suggest such a process.

Gillies Journal Article

The Gillies article is entitled "A Tissue-specific Transcription Enhancer Element is Located in the Major Intron of a Rearranged Immunoglobulin Heavy Chain Gene." As the Examiner states, "Gillies is primarily concerned with the enhancer element,

not the actual production of the antibody." The article was written to explain the nature of DNA sequences in an intron found in a rearranged heavy chain immunoglobulin gene. The research show that these sequences had a role in transcription of that gene. The authors referred to those sequences as enhancer elements.

That article does not describe production of functional antibodies in non-antibody producing mammalian cells and the research was not designed to provide useful information on that problem. Hence, there would be no reason for someone who read the Cabilly patent to look to the Gillies article for any help in seeking a way to change the Cabilly process to produce functional antibodies in non-antibody producing mammalian cells.

Gillies and coauthors were studying how mammalian cells naturally produce antibodies. In order to study the DNA located in the intron of an immunoglobulin heavy chain gene, Gillies cloned a genomic heavy chain gene and inserted that gene into a mammalian cell that did not naturally produce the heavy chain. Only in that way could Gillies study the effects of alterations in the DNA sequence of that gene. The heavy chain gene that they used was a functionally rearranged immunoglobulin heavy chain gene from MOPC141 tumor cells that they had previously shown could be expressed at low levels in a transfected mouse L cell. (Gillies p. 718). Gillies described subcloning that gene into a plasmid and transfecting a mouse myeloma line, J558L. That mouse myeloma line was said to have "lost the ability to express the endogenous immunoglobulin heavy chain gene, but continues to synthesize a λ light chain." (p. 718). Gillies described how that cell line expressed high levels of the specific immunoglobulin heavy chain γ2b. Gillies also noted (p. 718):

> "Apparently, this heavy chain can form an immunoglobulin molecule with the λ light chain of myeloma J558L, because the light chain was immunoprecipitated from cell extracts with heavy chain anti-sera and equimolar amounts of heavy and light chain were secreted into the culture medium. (Figure 2A, lane 14)."

Gillies did not describe the nature of that "apparent" "immunoglobulin molecule." They did not describe that molecule as an antibody. They did not test it for antigen binding. Nor did they further characterize its structure other than to note that the light chain was bound in some undescribed fashion to the heavy chain.

A person skilled in immunology and genetic engineering who read the Gillies article in 1983 would not have understood it to teach that transfection of an exogenous heavy chain gene from one source into a mammalian cell line (that expressed an endogenous light chain gene) produced a functional antibody. Prior to the invention made by appellants, no one (including Cabilly) had described making a functional antibody by transfecting a heavy and light chain gene into a mammalian cell, expressing those genes, and secreting an assembled antibody capable of specifically binding antigen. If Gillies and coauthors had accomplished that feat in July 1983, they certainly would have said so. A skilled person would have understood the Gillies article to disclose only what actually happened, namely that the exogenous heavy chain gene was expressed and "apparently" formed some uncharacterized immunoglobulin molecule with the endogenous light chain. There is no basis for concluding that a skilled person in 1983 would have understood the article to say that a fully assembled, functional antibody capable of specifically binding antigen had been produced.

Indeed, the Gillies article, like the Cabilly patent, would have discouraged the search for a method of producing functional antibodies by transfecting a light and a

heavy chain gene into a mammalian cell. A person would have been discouraged from using the mammalian cells of Gillies, namely mouse myeloma line J558L, that endogenously produced a light chain. Such a person would be concerned that the endogenous light chain might form an apparent "immunoglobulin molecule" with the exogenous heavy chain. This would interfere with assembly of a functional antibody by assembly of the exogenous heavy chain and the exogenous light chain. A skilled person would have been surprised by appellants' invention which showed that transfection of an exogenous light and an exogenous heavy chain into the mouse myeloma line J558L would lead to the direct production of antibodies specifically binding to antigen. (Application Example 1).

The Combination Of The Cabilly Patent And The Gillies Article

The Examiner asserted that Cabilly's disclosure in view of Gillies made appellants' invention obvious. Cabilly discloses double transfection of heavy and light chain genes into bacteria cells. With respect to co-expression of those genes, Cabilly stated:

> "When heavy and light chain are coexpressed in the same host, the isolation procedure is designed so as to recover reconstituted antibody. This can be accomplished in vitro as described below, or might be possible in vivo in a microorganism which secretes the IgG chains out of the reducing environment of the cytoplasm." ((emphasis added) col. 13, lines 19-25.)

Gillies discloses transfection and expression of a heavy chain gene in mammalian cells.

Applicants' invention claims a method for producing a "functional antibody." That method includes co-transfection and co-expression of both the heavy and light chains in a mammalian cell. Claims such as 39 and 54 require that the heavy and the light chain be "intracellularly assembled together to form the antibody which is then

secreted in a form capable of specifically binding to antigen." There was no suggestion, explicit or implicit, of appellants' invention in either reference read alone.

There was also no basis in those references for combining their teachings. Neither Cabilly nor Gillies expressly or implicitly suggests combination with the other. As we have seen, while Cabilly asserted that reconstituted antibody can be recovered in vitro, he asserted only that it "might be possible" to recover antibody from co-expressed heavy and light chains in microorganisms. Cabilly provided absolutely no suggestion that co-expression is even "possible" in the mammalian cells used in Gillies. Similarly, Gillies provided no suggestion that an exogenous light chain gene could be co-transfected and co-expressed with the heavy chain gene in vivo as Cabilly said "might be possible" in microorganisms. And, there was absolutely no mention in Gillies that pursuing such a method would yield a functional antibody.

There is also no basis in those references for finding that a person of skill in the art would have had a reasonable expectation of success. To provide such an expectation in 1983, the Cabilly reference in view of Gillies must have lead a person of skill in the art to believe that the mammalian cell would express both exogenous genes, that the two expressed proteins would be assembled together, that the assembled chains would be secreted, and that the secreted chains would be functional in binding antigen. In 1983, if a person had a suggestion to try co-expression in a mammalian cell, that person might have hoped that the experiment would succeed in producing functional antibody, but he or she would not have reasonably expected that each of the foregoing steps would

be successfully performed resulting in the successful production of functional antibody.* Skill in the art of genetic engineering and immunology is exactly what would have keep an inventor from expecting, as opposed to hoping, to succeed in such a quest.

As detailed above, the Cabilly patent, despite having disclosed mammalian cells as potential hosts for its expression vectors, only mentioned microorganisms when discussing the possibility of recovering antibody in vivo from co-expression of the heavy and light chain genes. Cabilly provides no basis for expecting success with appellants' process.

As discussed above, Gillies detailed work done to identify and understand the operation of genetic elements that acted to enhance the expression of gene segments. A gene coding for an antibody heavy chain was transfected into a mammalian cell. That gene was expressed and heavy chain protein was detected. Functional antibody could not have been produced with the host cells and vectors disclosed in Gillies. The endogenous light chain had a variable region that was specific for a different antigen than the antigen for which the exogenous heavy chain was specific. Therefore, it would have been impossible for the two chains to assemble together to form a functional antibody. A person of skill in the art who read the Gillies article in July 1983 would not have assumed that functional antibody was produced from the transfected heavy chain gene and the endogenous light chain gene. Indeed, in July of 1983, no one had ever made a functional antibody in vivo by transfecting genes into host cells. The accomplishment would have been significant, and not one that the authors would have forgotten to mention.

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* Of course, "Obvious to try" is not the test, or even a proper consideration, in determining whether an invention is obvious.

Accordingly, Gillies likewise provides no basis for a reasonable and skilled person to expect that a fully assembled functional antibody capable of binding antigen had been produced with appellants' process. Even if, as in Gillies, one exogenous gene was expressed in the mammalian cell, there would have been no reasonable certainty that two exogenous genes would both be expressed with the resultant chains being assembled and then secreted in functional form.

The Cabilly patent and the Gillie article must be understood as they would have been by a reasonable skilled person, namely in light of the whole prior art. Prior to this invention, it was not even believed that one exogenous chain would always be expressed, let alone assembled with a second immunoglobulin chain. For example, Oi et al., PNAS, Vol. 80, pp. 825-29 (1983) (A copy is attached as Appendix J.) A mouse myeloma cell supported expression of a transfected immunoglobulin gene. However, a rat myeloma cell line which expresses and secretes an endogenous light chain, when treated in the same manner as the mouse myeloma, did not support expression of a transfected immunoglobulin chain gene.

Prior to this invention, the art as a whole taught that a non-producing cell would not necessarily express a transfected exogenous immunoglobulin chain gene. Thus, a skilled person certainly would not have had a reasonable expectation that such a cell would successfully express, assemble and secrete the product of that first exogenous gene with the product of a second exogenous gene.

Even if a skilled person would expect that co-expression of two exogenous genes resulted in the expression, assembly, and secretion of the heavy and light chains, that person would not necessarily expect that the secreted molecule would be a functional

antibody. The assembly may not have the complex tertiary structure that is critical to specific binding of antigen. (See Declaration of Morrison, dated August 18, 1993 in application 07/893,610.)

The Secondary Considerations

Finally, in determining obviousness, the Examiner must consider any objective evidence of nonobviousness, such as the failure of others, unexpected results, and praise from others in the field.* There was cogent evidence of each of these factors.

Failure of Others

The Cabilly patent is an example of a failed attempt to produce functional antibodies directly from cells that had been transfected with DNA coding for the light and heavy chains. Cabilly was attempting to produce antibodies from such cells. Cabilly failed.

Those skilled in the art have recognized the failure of the Cabilly approach to produce properly assembled antibodies. In 1988, Arne Skerra and Andreas Pluckthun commented on attempts to express immunoglobulins according to Cabilly. Science, Vol.

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* Minnesota Min. and Mfg. v. Johnson & Johnson, 976 F.2d 1559, 1573, 24 U.S.P.Q.2d 1321, 1333 (Fed.Cir. 1992); Perkin-Elmer Corp. v. Computervision Corp., 732 F.2d 888, 895-96, 221 USPQ 669, 675 (Fed.Cir. 1984). As the court said in Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538-39, 218 USPQ 871, 879 (Fed.Cir. 1984):

> "Thus evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness. . . Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record. It may often establish that an invention appearing to be obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art." (Citations omitted).

240, pp. 1038-1041 at p. 1038 (May 20, 1988) (A copy was attached to the Supplemental Preliminary Amendment And Statement, dated May 15, 1991, in application 07/675,106):

> "Despite numerous investigations, the expression of functional whole antibodies or functional antigen-binding fragments of antibodies has not been reported for any bacterial expression system, and the chance of designing such an expression system has been viewed pessimistically[]....The purification of active antibodies or antibody fragments from yeast or any other microorganism has not been reported. In E. Coli, the antibody protein could be produced only in a non-native state[], and refolding experiments led to only a small percentage of correctly folded recombinant antibodies. Moreover, it is difficult to purify the native protein from non-native contaminants, which complicates accurate measurements of binding constants, folding yields, and spectral properties."

In that same issue of Science, Better et al. (pp. 1041-43 at p. 1041, a copy of which was attached to that Supplemental Preliminary Amendment) stated that "Escherichia Coli has been used to produce individual immunoglobulin chains internally that are not properly folded ..." Better cited to the 1984 article by Cabilly and others, Cabilly et al., Proc. Natl. Acad. Sci. USA, 81, pp. 3273-77 (1984) (Cabilly R) and Boss et al., Nucleic Acids Research, 12, pp. 3791-3806 (1984) (a copy of which was attached to that Supplemental Preliminary Amendment), for support. Likewise in 1987, Antonino Cattaneo and Michael S. Neuberger reported that "the introduction of vectors driving expression of immunoglobulin cDNAs into yeast or Escherichia Coli hosts has not resulted in effective antibody production--problems being encountered both with efficient assembly and with secretion (Cabilly et al., 1983; Boss et al., 1984; Wood et al., 1985)." EMBO J., Vol. 6, pp. 2753-58 at p. 2753 (1987) (A copy of which was attached to that Supplemental Preliminary Amendment).

In contrast, appellants achieved significant binding antibody production by co-transforming non-antibody producing mammalian cells. The production of a significant and useful amounts of antibodies capable of specific antigen binding is central to applicants' invention. Specificity and its attendant advantages are discussed throughout applicants' specification. The first sentence in the Description of the Specific Embodiments begins, "[n]ovel methods and compositions are provided[] for production of polypeptide products having specific binding affinities for a predetermined ligand...." (p. 2, lines 32-24)

Unexpected Results

The appellants submitted evidence showing that, not only was it unexpected that a non-antibody producing mammalian cell could produce any functional antibody by assembling light and heavy chains and secreting an antibody, but that the process produced antibodies in an amount 42 times greater than Cabilly. (Declaration of Sherie L. Morrison, dated August 18, 1993 in application 07/893,610). This is a 4200 percent increase in yield over Cabilly. Dr. Morrison's declaration explains laboratory data that establish an unexpectedly high yield of functional antibody.

Applicants' initial analysis of the expression product of their co-transformed cells was performed without attention to maximizing yield, but rather merely to demonstrate specific binding. Nonetheless, that analysis demonstrated an unexpectedly high 32% yield of active, assembled antibody. (Morrison Declaration, ¶ 5). In fact, that yield is likely a significant underestimate of the amount of correctly assembled antibody produced. (Morrison Declaration, ¶ 8.)

Cabilly's approach to "recombination" of light and heavy chains resulted in an extremely low level of antibody formation -- only 0.76% of the chains are reported as having "recombined." (col. 27 lns. 18-27). Appellants' achieved a yield that is over 42 times greater than the amount of active antibody that Cabilly reported and, therefore, is unexpectedly high when compared with Cabilly's .76% yield. One might expect an improved yield when expressing a mammalian gene in a mammalian environment as applicants did. Even expecting to double the yield might be reasonable. However, applicants have obtained a wholly unexpected improvement in yield that is 42 times the yield cited in the Cabilly patent. This result is of both statistical and practical significance. (Morrison Declaration, ¶¶ 9-10.)

While appellants' yield is likely understated, Cabilly's 0.76% yield may be overstated. Cabilly's 0.76% yield is based on an estimate of the levels of heavy and light immunoglobulin chains in the reaction mixtures and on an antigen binding assay. (col. 27, lns. 11-16). Not only is this calculated yield dubious by virtue of its reliance on an estimate with unknown associated error, but the calculation also used as a background number the binding measured for cells producing light chains only. A more accurate background number to correct for non-specific binding would have been the antigen binding for cells producing only heavy chains because it has been found that heavy chains alone will bind antigen in the absence of a complementary light chain. Ward et al., Nature, vol. 341, pp. 544-46 (1989). (A copy is attached as Appendix K.) That number would likely have been much higher than the light chain background number and would have resulted in a lower percent yield. Even given this potential for overestimating percent

recombination, Cabilly calculated obtaining only a fraction of one percent of the antibody protein in active form.

Whether or not Cabilly's yield is an accurate estimate, applicants' yield is so much larger as to be an unexpected result. Such results weigh heavily against a finding of obviousness.

Praise for the Invention

Third, the appellants introduced evidence showing that this invention was praised by others skilled in the art when they learned of it. In 1984, Michael Boss, congratulated one of the present inventors for, in essence, beating him to the production of functional antibody by using mammalian cells instead of bacteria (Morrison Declaration, ¶ 14). Michael Boss is one of the inventors of U.S. patent 4,816,397 entitled "Multi chain Polypeptides or Proteins and Processes for Their Production." The Examiner relied on that patent as an alternative primary reference to the Cabilly patent in supporting a now-withdrawn rejection under Section 103. (Examiner's Action, November 1, 1994, application 08/266,154, Paper 37). Such praise for the invention from skilled people is another secondary consideration that supports a finding of nonobviousness.*

The Legal Standard

The appellants are entitled to a patent unless the teachings of the cited prior art references established a factual basis for finding the claimed invention to be prima

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* Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143-44 (Fed.Cir. 1985).

facie obvious over those teachings.* If the teachings of the prior art do not establish a factual basis for this finding, the rejection must be reversed.

Because the appellants made the invention prior to October 19, 1983, this appeal requires the Board to determine what the prior art would have fairly taught an ordinarily skilled person in October 1983. The teaching of the prior art must be evaluated in its entirety to determine what it would fairly teach a skilled person at that time.** Section 103 requires that the prior art must disclose some, suggestion, motivation or reason that would lead a person of ordinary skill to make the invention and must contain a basis for finding that this person would have had a reasonable expectation of success.***

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* In re Ochiai, 71 F.3d 1565, 1569, 1572 , 37 U.S.P.Q.2d 1127, 1131, 1133 (Fed. Cir. 1995); In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed.Cir. 1992) ("If examination at the initial stage does not produce a prima facie case of unpatentability, then without more the applicant is entitled to grant of the patent."); In re Piasecki, 745 F.2d 1468, 1473, 223 USPQ 785, 789 (Fed. Cir. 1984).

** This means "[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to a full appreciation of what such reference fairly suggests to one of ordinary skill." It is the prior art as a whole that reveals the "accepted wisdom" against which nonobviousness or obviousness is to be decided. In re Hedges, 783 F.2d 1038, 1041, 228 USPQ 685, 687 (Fed.Cir. 1986).

*** In re Lalu, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed.Cir. 1984) ("In determining whether a case of prima facie obviousness exists, it is necessary to ascertain whether the prior art teachings would appear to be sufficient to one of ordinary skill in the art to suggest making the claimed substitution or other modification. In re Taborsky, 502 F.2d 775, 780, 183 USPQ 50, 55 (CCPA 1974). The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). If a person of skill would find it necessary to use the teachings of more than one prior art to obtain the invention, the prior art must suggest or give a reason for combining the teachings of those references. In re Grabiak, 769 F2d 729, 732 (Fed.Cir. 1985) ("We repeat the statement of *In re Bergel*, 292 F.2d 955, 956-957, 130 USPQ 206, 208 (CCPA 1961), that: The mere fact that it is *possible* to find two isolated disclosures which might be combined in such a way to produce a new compound does not necessarily render such production obvious unless the art also contains something to suggest the desirability of the proposed combination." (Emphasis in original)).

As summarized in In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed.Cir. 1991):

> "Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. See In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure."

It is not sufficient that the prior art provided a basis for finding that a skilled person would have thought that it might be possible to produce the invention.* Both the suggestion, explicit or implicit, and the reasonable expectation of success must be found in the prior art read without benefit of the inventor's disclosure. It is improper to employ hindsight.

CONCLUSION

Appellants have demonstrated that there was not a proper basis for concluding that this invention was prima facie obvious at the time it was made in 1983.

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* Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380, 231 USPQ 81, 91 (Fed.Cir. 1986)("The earliest four of the eight articles, on the other hand, although clearly prior art, discuss *production* of monoclonal antibodies—admittedly old after Kohler and Milstein showed how to product them—but none discloses sandwich assays. At *most*, these articles are invitations to try monoclonal antibodies in immunoassays but do not suggest how that end might be accomplished. To the extent the district court relied upon these references to establish that it would have been *obvious to try* monoclonal antibodies of 10^8 liters/mole affinity in a sandwich immunoassay that detects the presence of or quantitates antigen, the court was in error. *See Jones v. Hardy*, 727 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed.Cir. 1984) ("Obvious to try" is improper consideration in adjudicating obviousness issue.)" (footnote omitted)); In re Antonie, 559 F.2d 618, 620, 195 USPQ 6, 8 (C.C.P.A. 1977).

The Appellants have shown that the prior art as a whole did not suggest this process, explicitly or implicitly, and did not provide a reasonable basis for a skilled person to expect that the process would work. Rather, appellants have shown that the prior art as a whole would have led skilled people away from this invention. Appellants have also shown that the primary Cabilly reference was a practical and technological failure, that in contrast, their invention provided a totally unexpected, unpredictable result -- at least a 4200 percent increase in antibody yield over Cabilly, and that their invention was praised by a skilled competitor. The preponderance of the evidence clearly rests on the side of patentability. The Examiner has failed to carry the burden of persuasion.

The rejection is erroneous and should be reversed.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Sherie L. Morrison, *et al.*
Serial No.	:	08/266,154
Filed	:	June 27, 1994
For	:	RECEPTORS BY DNA SPLICING AND EXPRESSION

Palo Alto, California
July 14, 2000

DECLARATION REGARDING RECORDS

I, VICKI S. VEENKER, declare that:

1. Enclosed is an authentic copy of the Appeal Brief filed September 25, 1996 in the above-referenced application, which copy was made from Fish & Neave's records concerning the prosecution of that application in the U.S. Patent and Trademark Office.

2. I declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that all these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful, false

statements may jeopardize the validity of the application or any patent issuing thereon.

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Applicant : Sherie L. Morrison, et al.

For : RECEPTORS BY DNA SPLICING AND EXPRESSION

Serial No. : 08/266,154

Filing Date : June 27, 1994

EXPRESS MAIL CERTIFICATION

"Express Mail" number EF056114785US.
Date of Deposit September 25, 1996

I hereby certify that this paper/fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Honorable Assistant Commissioner for Patents, Box PCT, Washington, D.C. 20231.

Joshua Martin

Enclosures: Transmittal Letter in Duplicate
Amended Appeal Brief in Triplicate
Postcard